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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/678,145 | 10/06/2003 | Walter C. Babcock | PC26122A | 1094 |

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| EXAMINER | |
|---|---|
| ALSTRUM ACEVEDO, JAMES HENRY | |
| ART UNIT | PAPER NUMBER |
| 1616 | |
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| 07/30/2009 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/678,145 | BABCOCK ET AL. | |
| | Examiner | Art Unit | |
| | JAMES H. ALSTRUM ACEVEDO | 1616 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *01 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-4,7,8 and 10-20* is/are pending in the application.

4a) Of the above claim(s) *15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 7-8, 10-14, and 16-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

**Claims 1-4, 7-8, and 10-20 are pending.** Applicants previously cancelled claims 5-6 and 9. Applicants have amended claims 1 and 3. Claim 15 is withdrawn as being drawn to a non-elected invention. Claims 16-20 are new. Receipt and consideration of Applicants' amended claim set submitted on April 1, 2009 and remarks/arguments submitted on April 1, 2009 and December 29, 2008 are acknowledged. All rejections not explicitly maintained in the instant office action have been withdrawn per Applicants' claim amendments. Applicants' claim amendments have necessitated new grounds of rejection set forth below.

### *Specification*

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

**Claims 1-4, 7-8, 10-14, and 16-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sikorski et al. (WO 00/38722; "Sikorski", IDS reference) in view of Gurtler et al. (U.S. Patent No. 5,773,021; "Gurtler", of record), Mulligan et al. (U.S. Patent No. 5,128,142; "Mulligan", of record), Rowe et al. (US 2003/0099708), and Jin (US 2004/0001888).**

### *Applicant Claims*

Applicants claim a composition comprising (a) a solid amorphous adsorbate comprising a cholesteryl ester transfer protein inhibitor that is adsorbed onto a substrate, selected from the group consisting of inorganic oxides, zeolites, clays, and activated carbons, wherein the substrate surface has a surface area of at least 20 $m^2/g$ and 60% or more of the CETPI is amorphous (i.e. a "major portion" is amorphous, see definition of "major portion" in paragraph [1073] in specification) and (b) an HMG-CoA reductase inhibitor (e.g. atorvastatin). In some embodiments the composition further comprises a

concentration-enhancing polymer (e.g. cellulose acetate trimellitate) and/or a dissolution enhancing polymer (e.g. PVP).

***Determination of the Scope and Content of the Prior Art (MPEP §2141.01)***

Sikorski teaches combinations of an HMG CoA reductase inhibitor and CETP inhibitor (abstract) that are suitable for the treatment of cardiovascular disease. **The elected CETP inhibitor is specified ("C-12" on page. 18).** The elected atorvastatin is disclosed (Table 2 page 21). Specifically in Table 3 on page 38, Sikorski teaches **a composition comprising both the elected CETPI and atorvastatin.** Sikorski's claim 7 also specifies the combination of a CETPI with atorvastatin. **Tablets are specified (page 26, line 30).**

Gurtler teaches an insert polymeric material matrix for prolonged and control release in which a medicinal substance is incorporated (abstract). Adsorption onto a support is disclosed (column 3 lines 25-32) as an exemplified pre-treatment of the medicinal substrate. **Cellulose acetate trimellitate is specified** (column 3, line 46). Other suitable physical support polymers are also disclosed, including **various substituted neutral celluloses** and other polymers (col. 3, lines 41-54).

Mulligan et al teach a controlled release formation comprising **an active and an inactive substance *adsorbed* onto a cross-linked polymer** (abstract). The cross-linked polymer may be porous (col. 2, lines 10-13). The inactive substance may be water soluble to enhance the rate of active leached (column 2 lines 48-52). **Polyvinylpyrrolidone** is specified (column 3 lines 31-32), as a suitable inactive

substance. (On page 123 line 25 applicants disclose polyvinylpyrrolidone as a preferred dissolution-enhancing agent.).

Rower teaches that it is know that **one method of increasing the bioavailability of an active pharmaceutical ingredient (API) is to alter its structure, and that amorphous API has greater aqueous solubility than the corresponding crystalline API**, and consequently a greater bioavailability. For example, it has been shown that an amorphous API can have a greater bioavailability of about a factor of 5 relative to the corresponding crystalline form of said API ([0033]).

Jin teaches solid dosage forms for rapid dissolution of poorly soluble drugs, wherein the drugs are adsorbed onto **a solid porous powder support that can be silica ($SiO_2$), alumina (i.e. $Al_2O_3$), or cellulose derivatives** and wherein **the supports have surface areas greater than 100 $m^2/g$ and in some embodiments a surface area of 10 to 1,000 $m^2/g$** (abstract; [0028]-[0029], [0031], [0043], [0056]-[0058], and claims 8-11). The compositions may also comprise additional excipients and surfactants, wherein the ability of lipids and other surfactants to improve solubility, absorption, and bioavailability are fully preserved [0052]-[0053]. Suitable additional ingredients include microcrystalline cellulose, , starch, sodium alginate, etc. [0053]. The compositions can be formulated into various solid dosage forms (e.g. tablets, capsules, etc.) [0054].

***Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)***

Sikorski lacks the explicit teaching of amorphous drug, a composition in the form of an adsorbate, compositions comprising concentration-enhancing or dissolution-

enhancing polymers, and the specific group of substrates recited in Applicants' claims. These deficiencies are cured by the teachings of the combined prior art and what is commonly known in the art.

***Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)***

It would have been prima facie obvious to modify the composition of Sikorski to adsorb the drug composition disclosed onto or into a cross-linked polymer (e.g. a cellulose derivative) to obtain the benefits of a controlled-release formulation taught by (Gurtler) or onto other conventional solid supports, such as silica or alumina (Jin). It is noted that the cross-linked polymer disclosed by Gurtler is identified by Applicants as being a concentration-enhancing polymer and that Jin's teachings permit the inclusion of surfactants and other materials serving to enhancing the solubility and bioavailability of poorly soluble drugs. Thus, Sikorski's compositions as modified by the teachings of Gurtler/Jin would necessarily exhibit similar properties as Applicants' claims requiring a concentration-enhancing polymer in combination with a solid substrate. It would also have been prima facie to also utilize polyvinylpyrrolidone in Sikorski's compositions to obtain the benefits of the sustained release formulations disclosed by Mulligan. Sustained release is a kind of controlled release. Polyvinylpyrrolidone is taught by Mulligan as being a suitable substrate onto or into which an API may be adsorbed. Applicants have identified PVP as a dissolution-enhancing polymer. Thus, Sikorski's compositions modified to comprise PVP would necessarily exhibit API dissolution enhancing properties due to the presence of PVP as well as due to the high surface area of

the supports taught by Jin. In addition, the pore structure of Jin's supports would help ensure that crystallization did not occur and any drugs adsorbed therein or thereon remained in an amorphous state. It is noted that wherein polymers are used as the substrate onto which or into which an API is adsorbed, these substrates are often porous (e.g. Mulligan) and as such would necessarily have a higher surface area than non-porous substrates. Regarding whether the active substance is in an amorphous form or a crystalline form, it is common knowledge in the art that the amorphous form of a given API will have a greater aqueous solubility than its crystalline form and consequently a greater bioavailability. Enhancing the bioavailability of an API is a desirable result, as improved bioavailability enables one to prepare compositions requiring a lower amount of drug (Rower), which lowers productions costs and costs to the consumer, as well as reduces the likelihood of undesirable side effects. An ordinary skilled artisan would have had a reasonable expectation of successfully adsorbing Sikorski's drug formulations onto the substrate polymers taught by both Mulligan, Jin, and Gurtler, because the actives taught by Sikorski have low water solubility and the adsorption of low solubility drugs onto solid support surfaces (e.g. polymers, cellulose derivatives, silica, and alumina) is known (Gurtler and Mulligan) as a means of increasing bioavailability. Regarding the properties recited in claims 10 and 12, it is the Examiner's position that the compositions resulting from the teachings of the combined prior art and upon optimization of said teachings would necessarily exhibit the same or similar properties. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

### *Response to Arguments*

Applicant's arguments with respect to claims 1-4, 7-8 and 10-20 have been considered but are moot in view of the new ground(s) of rejection.

### *Double Patenting*

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

**NOTE:** Applicants have indicated they would file a terminal disclaimer over 11/566, 408 upon indication of allowable subject matter and have not traversed the below rejection of this copending application. This rejection is maintained below. The rejection over 10/173,987 (copending '987) is withdrawn, because copending '987 was abandoned on September 15, 2008. The rejection over 10/739,750 (copending '750) is withdrawn, because copending '750 was abandoned on November 12 2008.

**Claims 1-4, 7-8, 10, and 13 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 23, 29-31, 33, and 40-41 of copending Application No. 11/566,408 (copending '408) in view of Sikorski et al. (WO 00/38722).** Independent claim 1 of the instant application has been described supra. Independent claim 23 of copending '408 claims a unitary dosage form comprising (a) a solid adsorbate comprising a low-solubility drug that is a CETPI and (b) a concentration-enhancing polymer. Dependent claim 33 of copending '408 recites many of the same properties recited in claim 10 of the instant application. Dependent claim 41 of copending '408 recites the same CETPI as required by the claims of the instant application. The primary difference between the claims is that the claims of copending '408 do not specify that the CETPI is in combination with a HMG-CoA reductase inhibitor and that the substrate has a specific surface area. This deficiency is cured by the teachings of Sikorski, which establishes that both CETPI and HMG-CoA reductase inhibitors are known to be indicated for the treatment of the same conditions and are known in combination. Regarding the surface area deficiency, it would have been prima facie obvious to optimize the substrate surface area to control and modify the bioavailability of the adsorbed drug (i.e. more surface area = higher bioavailability for a given amorphous API). Therefore, a person of ordinary skill in the art at the time of the instant invention would have found claims 1-4, 7-8, and 14 *prima facie* obvious over claims 1, 9, 13-14, 23-24, and 31-32 of copending Application No. 10/739,750 (copending '750) view of Sikorski et al. (WO 00/38722).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

**Claims 1, 7-8, and 13 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 6-7, 9-10, and 12-13 of copending Application No. 11/795,743 (copending '743).** Independent claim 1 of the instant application has been described supra. Independent claim 1 of copending '743 claims a solid adsorbate comprising (a) a hydrophobic drug, and (b) a water immiscible lipophilic vehicle, and (c) a porous substrate. Dependent claims 6-7 and 10 specify that the hydrophobic drug is a CETPI and claim 7 identifies the CETPI required by the claims of the instant application as an example of a suitable CETPI. Dependent claims 12-13 of copending '743 recite that the dosage form comprising a solid adsorbate of claim 1 of copending '743 further comprises a HMG CoA reductase inhibitor and specifically identifies atorvastatin as a suitable comprises a HMG CoA reductase inhibitor. The primary difference between the claims is that the claims of copending '743 do not specify that the substrate has a specific surface area. This deficiency would have been considered prima facie obvious to optimize the porous substrate surface area to control and modify the bioavailability of the adsorbed drug (i.e. more surface area = higher bioavailability for a given amorphous API). Therefore, a person of ordinary skill in the art at the time of the instant invention would have found claims 1, 7-8, and 13 *prima facie* obvious over claims 1, 6-7, 9-10, and 12-13 of copending Application No. 11/795,743 (copending '743).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Response to Arguments***

Applicant's arguments filed 12/29/2008 have been fully considered but they are not persuasive. Applicants have traversed this rejection by arguing that it should be withdrawn, because copending '743 is a later filed application and Applicants believe the claims as currently written are allowable. Applicants pending claims are not allowable at this time as set forth above. This rejection is maintained.

***Conclusion***

**Claims 1-4, 7-8, 10-14, and 16-20 are rejected. Claim 15 is withdrawn as being drawn to a non-elected invention. No claims are allowed.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner is on a flexible schedule, but can normally be reached on M-F ~10am~5:30 pm, and Saturdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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